

A study of the allosteric inhibition of HCV RNA-dependent RNA polymerase and implementing virtual screening for the selection of promising dual-site inhibitors with low resistance potential

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Abstract

Structure-based pharmacophores were generated and validated using the bioactive conformations of different co-crystallized enzyme-inhibitor complexes for allosteric palm-1 and thumb-2 inhibitors of NS5B. Two pharmacophore models were added, a quantitative structure activity relationship (QSAR) models were developed based on using the values of different scoring functions as descriptors predicting the activity on both allosteric binding sites (palm-1 and thumb-2). QSAR studies revealed good predictive and statistically significant two descriptor models for palm-1 and thumb-2, respectively. Different docking protocols were examined for their validity to predict the correct binding poses of inhibitors inside their respective binding sites. Virtual screening was carried out on ZINC database using the generated pharmacophores, the selected valid docking algorithms and QSAR models to find compounds that could theoretically bind to both sites simultaneously.

Journal of Receptors and Signal Transduction 2017, January